Michael Gnant:

pushing the boundaries

Marc Beishon

Suppressing metastases by changing microenvironments doesn't sound like heartland research for a surgeon. But that hasn't deterred Michael Gnant, who presented a paper on this subject at last year's ASCO. He argues that cancer surgery risks reverting to a 'manual profession' unless others follow his lead and engage far more deeply with other disciplines, both in the clinic and in research.

The War Against Cancer – that grand scientific endeavour launched by President Nixon nearly 40 years ago – looks set for a major new offensive thanks to a windfall $1.3 billion awarded to the National Cancer Institute as part of the American Recovery and Reinvestment Act. Responding to an appeal to use the money imaginatively, the NCI has set out an ambitious programme that not only promises to delve into the depths of the cancer genome but stretches into completely new areas of science, including an examination of "how physical laws governing short-range and other forces, energy flows, gradients, mechanics, and thermodynamics affect cancer". But if we have learned anything from the past 40 years, it is that fast, fundamental breakthroughs are elusive, while important progress can be made by doing the right clinical and translational research, and organising cancer resources around best practice. With this in mind, health authorities without $1.3 billion to invest could usefully look to a small European country for evidence of effectiveness that stands out in several respects.

In Austria, 30% of breast cancer patients are now participating in clinical trials; for some time, many have been avoiding chemotherapy commonly given in other countries; and breast conserving rates are high, the number of mastectomies low. A conservative but effective approach to treatment has been combined with innovative trials work, such that from this country of just eight million people (plus some others from neighbouring countries), exciting results are now on the world stage. Most recent has been the use of bisphosphonates for not only tackling bone problems following endocrine treatment but also shedding more light on one of the great cancer mysteries – how and why cancer cells metastasise.

One of the key players behind Austria's emerging reputation in cancer is the professor of surgery at Vienna's Medical University, Michael Gnant – a surgical oncologist whose main focus has been on breast cancer. He is deputy chair of a department with 145 academic physicians and scientists, one of nine surgical heads at the 2,000-bed university hospital, and – very significantly in his view – the president of the Austrian Breast and Colorectal Study Group (ABCSG), which is largely responsible for the strikingly high participation rate in clinical trials.

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"The ABCSG is now a professional organisation with 50 associates and is like a small business in its own right; it takes up at least a third of my time," says Gnant. "With 19,700 patients now in clinical trials it's a huge operational task." Trials and other research certainly dominate Gnant's professional life – and he points out that, apart from driving the evidence base forward, a very active trials organisation also develops multidisciplinary working, across the country, and promotes international networking and a better standard of patient care. "I have invested a lot of effort in this because I wanted to convince people, from here to the Austrian Alps and beyond, that we really could not achieve much unless we joined forces in an academic network."

The fruits of his belief played out as spectacularly as is usually possible in the cancer world, when Gnant presented results from the ABCSG-12 bisphosphonate study at the American Society of Clinical Oncology (ASCO) conference last year. "This was the first large-scale investigation worldwide to demonstrate the significant value of the bisphosphonate, zoledronic acid, in breast cancer treatment," he says. "It improved the rate of recurrence-free survival by 35% in the study group – and it is posing all sorts of further research questions."

Gnant may ostensibly be a cancer surgeon, but as one of the younger generation of top oncologists he is pushing the boundaries of the role perhaps more than most with this kind of trial work. "I'm not as fascinated with technical excellence in surgery as some other surgeons are, as it is not an area where I feel we can develop much more. Of course there are new techniques to learn and it is always challenging to transfer knowledge to the next generation of surgeons, but for me by far the most dynamic area is integrating surgery as part of the multidisciplinary process."

His career path took him early on in the direction of the academic, research-based pursuit of

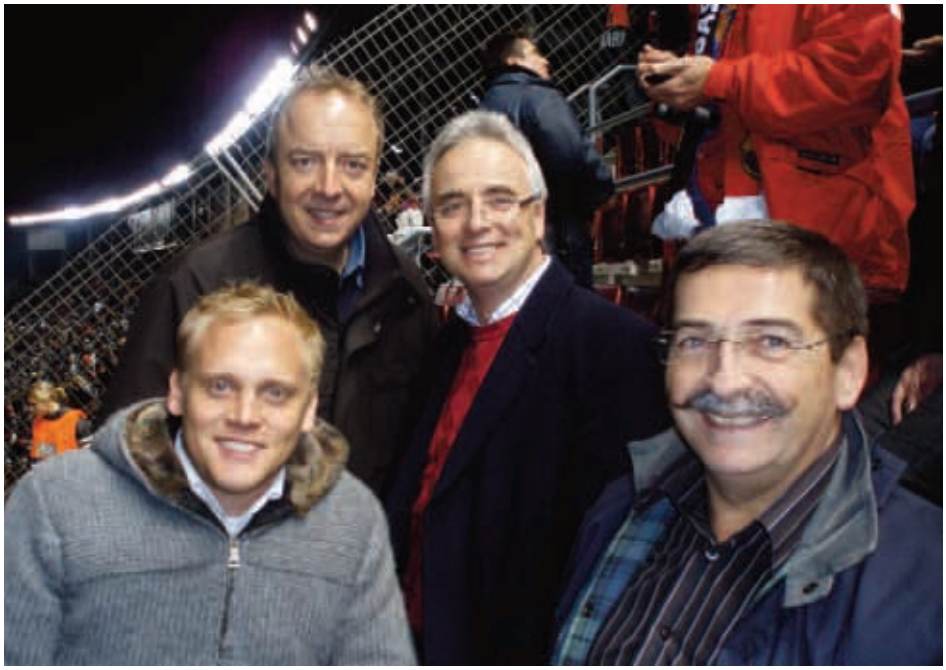
multidisciplinarity he now promotes as widely as possible. "Initially I wanted to be an actor," he says – such a calling now no doubt plays out in the numerous lectures and presentations he delivers, and he's in demand for far more than he can accept. "But the curiosity about how we work as an organism and a desire to help people took me into medicine. At first I became interested in intensive care, and then in my studies in Vienna and Munich I got involved in – and fascinated with – transplantation and the logistical challenge of procuring organs."

The novelty of a coordinator's job he took for a spell – including flying with organs on Learjets and receiving VIP treatment at airports – wore off when he realised it was like 'engine replacement by car mechanics'. "But the immunology part – stopping organs being rejected – took me into cancer, although of course it was for the opposite effect, where we wanted to kill cancers exploiting the same host-defence mechanisms."

Gnant completed general surgical training on rotation in Vienna – there is no surgical oncology board in Austria – and embarked on a career in cancer where carrying out experimental medicine has been as important as day-to-day clinical operations. By 1996, aged only 32, he had become head of both the breast cancer and experimental surgical oncology divisions at the medical university hospital. "I had become particularly involved with experimental treatments with late-stage patients, many of whom of course died, which fuelled my motivation in the field," he adds.

But the next year he was off to the US as a visiting scientist at the National Cancer Institute, where he worked in Stephen Rosenberg's surgical branch for two years on molecular biology and in particular gene therapy. "That was a hot topic ten years ago and we contributed substantial knowledge, but its clinical applicability has not really moved forward," he says.

An alternative would have been to move out of the university and set up a comfortable private surgical practice, as many doctors do in Austria. While Gnant does now run a personal office where he sees private patients (mainly for breast cancer, but also for pancreatic tumours as well as other high-level surgery), he only came back to Austria when the medical university created a professorship for him that suited his research ideals – and for a while he held the unusual title of chair of experimental surgical oncology. For the last nine years, he has built up the breast cancer research profile of the country, taken over the pancreatic cancer division and generally pushed colleagues as fast as possible in the direction of multidisciplinary working, national and regional networking, and greater international visibility.



Off duty. At Barcelona's Nou Camp stadium, after a hard day's work, with (from the right) Philippe Clezardin, research director at the French medical research body INSERM, Rob Coleman of the Cancer Research Centre, Sheffield, UK, and Max Kurz of the Science Agency Network, Switzerland

"I took on pancreatic work partly because breast surgery is often seen as not very technically challenging, and I learnt it from scratch. I also felt it would help establish myself more as a research surgeon and not just a 'breast cutter', by broadening my involvement with multimodal treatments."

Expanding on his views about surgery, he notes that it is not hard to find surgeons who can do a tricky procedure well. "The difference for me is between the ones who just cut a tumour out and say goodbye to the patients and those interested in integrating other treatments and looking after the patient. For the majority of

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my patients I will be their case manager, although I may not always carry out treatments if they relapse. This is the future for surgery – otherwise it will become de-academicalised and in danger of going back to the manual profession it once was – surgeons were once not considered to be doctors at all. I feel I have to look out for the future of my profession."

Adopting the case manager approach can be 'hugely' motivating for young surgeons, he adds, and of course in comprehensive cancer centres and academic settings, the issue of who provides what treatment is less controversial, although he reckons that this type of multidisciplinary working is rare – "You usually find one dominant discipline." In wealthy countries such as Austria, it can also be difficult for patients to find a physician willing to guide them through the cancer journey. "That can mean they tour round several of our many clinics without actually getting any treatment."

Austria's highly decentralised system also creates problems for surgical leadership, adds Gnant. "As we get older we inevitably develop narrower, more specialist skills – but if you leave an academic setting to progress your career and become head of a team at a community hospital, you may lack the broad knowledge needed for good leadership. That's a problem for all branches of medicine though." Another issue in cancer, he adds, is that despite success in promoting the multidisciplinary approach around the country through the ABCSG and trial work, there are clinics where there is considerable tension between surgeons and medical oncologists, and also places, particularly near the German border, where gynaecologists and not oncologists have assumed leadership in breast cancer, and not always to the benefit of patients in either country, he states.

"These are not just local issues – I was at a meeting in Miami recently where breast surgeons were complaining fiercely about their lack of impact and talked about setting up their own trials group, as they feel they've been marginalised by the drug community."

Gnant would like to see his country move in the direction of the UK, where the NHS has set targets for shorter waits to see specialists and receive cancer treatment, and where staff and patients migrate to specialist centres and there is little expectation of always having a clinic on the doorstep. "It would be seen as a big scandal here if people had to travel far," he says. "I also see the eastern European counties that have just a few larger cancer centres as having an opportunity to avoid our mistakes and centralise expertise, but they do of course suffer from lack of resources at present. We cannot go on having 100 hospitals for just eight million people in a world where two thousand research articles on breast cancer are published each week."

He adds, "I'm also unhappy that the medical community here seems to have lost out to the economists in discussing reform. We ought to be making the case for more specialisation through evidence of factors such as quality, as in cancer we have clearly defined outcome parameters such as local cure and relapse rates – this is easier to judge than in fields such as geriatrics."

The ABCSG was founded in 1984, and despite the ongoing issues Gnant highlights, has made substantial progress in uniting oncologists around the country and some in Germany, especially in breast cancer (see also www.abcsg.at). The rationale for combining two of the more common cancers – breast and colorectal – in one cooperative group, has already long been made in the US by the National Surgical Adjuvant Breast and Bowel Project, funded by the NCI, which has a 50-year history and enrolled more than 110,000 women and men in clinical trials, although at nowhere near the per capita rate achieved in Austria.

As Gnant notes, there was also a view that it was important to look further afield than Germany for progressive models. "The German system has traditionally been more hierarchical and vertical – one boss directing often very senior physicians can be very demotivating. I am in favour of a team

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approach and also encourage young researchers to travel widely to the US, UK and other countries outside of Austria and Germany. Yes, Munich for example is a global leader in some research and there are many extremely impressive researchers in the country, but I now conduct all my lab meetings in English and have stopped publishing in German – English has won and that's it. And getting involved in global research can be wonderfully effective."

What has proved effective for Gnant has been building on an early interest in adjuvant treatment for breast cancer. "I realised that just cutting out a tumour was not good enough for patients or for me, and that triggered my interest in endocrine interventions in particular, and it also fits with my philosophy of taking care of women after surgery. Mostly we have been able to show that there is a greater gain by working with medical oncologists and others, and sharing patients and studies, although of course there are still big arguments in some places."

Gnant's key message about breast cancer is that the vast majority of patients under his care can expect excellent outcomes – "90% have 10-year survival thanks to our good early detection and local treatment. Of course many women are very fearful, but I try to put the risk into perspective – I spend a lot of time on communication." Endocrine treatment is designed to help eliminate part of the long-term risk for the majority, who have hormone-responsive tumours, and he feels very strongly that there has been too much emphasis on also adding chemotherapy, with toxic and other side-effects, for a small gain. "Medical oncologists tell us we need to hammer a nail in everywhere and to save lives and we must put that toxic burden on patients. But we end up by losing some to complementary therapy – and that's our fault, not the patients' fault. We need to get them back." Not for nothing is Austria known now as the 'endocrine country' – "We have been treating women without chemotherapy for 20 years with great success."

Endocrine treatment is a standard for post-menopausal women, and Gnant has been leading research into the currently uncertain area of pre-menopausal patients and aromatase inhibitors, which, he says, are more effective and better tolerated than tamoxifen. But aromatase inhibitors can cause substantial bone loss, which is where the bisphosphonate story comes in. Gnant is leading the pivotal ABCSG-12 study, which has recruited 1,800 premenopausal women with early-stage, hormone-responsive breast cancer from Austria and 150 from Germany, and is designed to test the effectiveness of different endocrine treatments for younger women. The effect of bisphosphonates (in this case zoledronic acid) for bone protection had been known for some time, but the mechanism has only recently been demonstrated. Patients in one arm of the study received this additional treatment.

Results show that the aromatase inhibitor (anastrozole) worked as well as tamoxifen, and the addition of the bisphosphonate had significant bone-protective effects. But it is also now seen to have direct antitumour and antimetastatic effects. "It has been known for some time that bisphosphonates have these effects," says Gnant, "but the large doses used in animals could not be replicated in humans. Many of us expected that by using a bone-active drug we would, if we were lucky, see a reduction in bone metastases, the most common remote site for breast cancer, and indeed we've seen a reduction of a third. But what's even more

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exciting is that we have observed the same or even more reduction in metastases in other distant sites such as the liver."

As Gnant adds, the mechanisms for this effect are not well understood yet, but it was always unlikely, in his view, that tumour cells would simply circulate around the body and lodge in places like the liver and suddenly wake up years later without metabolism. "What we now think, and we're waiting for more evidence, is that certain populations of tumour cells – tumour stem cells – drive malignant disease and have the ability to resist drugs. But they can also spread early and go into a quiescent state in a region of the bone marrow, which is a 'sanctuary' for them as well as normal stem cells. Again, they wake up for reasons we don't know well – and what happens then depends on the type of microenvironment they find. You can't hunt them down with chemo- or endocrine therapy as they're typically indistinguishable from normal stem cells, and more like sleeper cells from Al Qaeda. But we can change their microenvironment – which is what bisphosphonates do, basically as a side-effect – through the primary function of inhibiting bone resorption. You may also then deprive the tumour cells of growth factors and they might just do what they are programmed to do and go into apoptosis and kill themselves, rather than having the perfect conditions to grow, differentiate and spread daughter cells to other organs."

There are other trials of bisphosphonates in treating prostate, lung and other tumours that should, says Gnant, expand their role in both early- and late-stage disease, and it is not hard to see why he is in demand on the lecture circuit at present to talk about this story. Like some of the best narratives, he traces its roots way back – to a paper by Stephen Paget in the *Lancet* 120 years ago on the 'seed and soil' hypothesis of metastasis – where the seed is the tumour cell and the soil the microenvironment. "We could begin to explain some of the issues we've seen for decades, such as why colorectal cancer sometimes bypasses the obvious site, the liver, and instead spreads to the lung. Surgeons know that people with cirrhosis suffer less frequent liver metastases – it's the same cancer so it is something to do with the tissue that receives the cells. And we'll find agents other than bisphosphonates to pursue this work."

Overall, Gnant feels that adjuvant treatment has been the biggest factor in the reduction in mortality seen in breast cancer (in Austria, he says, it has dropped by about a third over 15 years). He agrees that survival rates are levelling off and the struggle to gain a small increase can mean huge, expensive studies that funders may not be prepared to back. "There may also be more simple things we can do, such as helping patients to comply with their prescriptions – about half don't take drugs as prescribed, and eliminating this problem may give us a few per cent gain. We also need to focus more on low-risk disease, which is the majority, and on communications between patients and doctors about risk and proper follow-up and case management.

"And progress can cause problems. We know for example that MRI is valuable in some situations, but it's well documented that it's leading to overdiagnosis and an increase in mastectomy rates. We need more caution about how we translate research into practice – we are often too quick to demand that a new therapy or technique is provided for everyone, but with MRI we have a tool that has led to worse treatment."

Talking of mastectomy, Gnant says he has not carried out a single preventive procedure in his career of more than 2,000 breast operations so far. "The proportion with very high risk is really quite small and there are other things we can do." This includes chemoprevention with tamoxifen, which has failed to be successfully

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introduced clinically for a variety of reasons, despite actually being proven 'level one' evidence, he notes. "I also think that what women are told about breast reconstruction is not true. You may get a good shape but not sexual arousal, for instance. And from what we know about dormant tumour cells, you may not be cutting your risk anyway – and to put it bluntly, some women would rather die with their breasts on. Only one in ten women who see me about such a mastectomy will eventually go for it."

On this issue he disagrees with another research-driven breast surgeon profiled recently in *Cancer World* (March–April 2009), Emiel Rutgers in Amsterdam, who has long had a preventive mastectomy programme. "I am also not as enthusiastic as Emiel is about how quickly we should be implementing gene array profiling. I'm a member of the Breast International Group and supporter of the MINDACT trial, which is asking the right questions about identifying women who do not need expensive chemotherapy. It would be terrible if it failed, as it could curtail future funding from the European Union and other bodies. But it is complex, it is taking a long time, and the collecting of fresh tissue is a nightmare, especially in small centres." In the very large HERA (HERceptin Adjuvant) trial, he notes that researchers have managed to collect only 1,100 tumour blocks from 5,500 patients.

"It's unethical for us not to do more to collect samples, not least because it will just make it longer to learn from translational research," he says.

He notes the rush to market gene array diagnostic tools, and expects that at some point they will be useful in helping with the 15%–20% of intermediate cases. "But for clear-cut high- and low-risk cases we don't need an assay that's more expensive than the treatment," he says, and he mentions a colleague in the US who has been ordering such assays at several thousand dollars a time – but is not yet basing treatment decisions on the results. "We need to apply the same scrutiny with any new approach as we are doing with bisphosphonates, and properly fund the right prospective trials and be patient. In any case, in Austria it is not an issue, as we are not using chemotherapy in the first place." He adds that work in Vienna on gene arrays will be confined to the research setting for the time being. "I've had wonderful genomic slides in my presentations for 10 years, but have yet to use them in the clinic."

Gnant also says Europe faces more problems from industry intervention. "I'm not a socialist, but I agree with more state funding – in the US, half of breast cancer research is funded by government, but in Europe it is less than 10% and every university has to have spin-off companies. We do need to speed things up, especially where there is very pressing medical need, as with HIV, but we also have to keep in place the right processes."

Family circle. A hot drink on a cold night with wife Claudia and youngest daughters Lisa and Anna

Despite misgivings about too much haste, he'd be the last person to do less research – he describes himself as a self-confessed 'clinical trials junkie'. But along with the right processes to conducting research, he emphasises the need for a more holistic approach to delivering care within trials, as participation in trials is being held back by reservations that evidence-based medicine is too technocratic and impersonal.

He does not pull any punches on other issues, such as the certification of breast centres. "Sometimes breast centres are funded or declared for the sole purpose of marketing or increasing patient referrals," he wrote in *Breast Care*, "and such abuse is tricky to detect and virtually impossible to prohibit." Gnant notes that in 2006 there were 100 certified breast centres in Germany and just three in Austria – but the latter's centres had a much higher clinical trials participation rate – "a most effective way to provide quality assurance" – and so the numbers are unlikely to reflect a difference in care standards.

The driving force of trials also plays out in his views on research agencies, for example the European Organisation for Research and Treatment of Cancer (EORTC). "Every day I randomise twice as many patients in my tiny country as they do – why is that? We need more energy from more people and not organisations led for too long by the same people that are more like old boys' clubs. We need to constantly improve." Ideally, he would like to see the often mentioned idea of a European cancer research institute, and says he's been involved in reviewing current EU funding streams. "A lot of money goes to certain institutions," is his rather guarded comment.

On guidelines and opinion (which is where he puts the influential St Gallen consensus, where he is a panel member), he is firm that they are just 'defaults' that describe common ground, and no substitute for understanding each patient. "On my website I use this saying from Michael Baum [another outspoken breast surgeon]: 'The art of medicine begins where standards end.'"

Finally, while very much in favour of patient empowerment, he does feel that advocacy groups can sometimes be counterproductive. "I find that patients can go to meetings and come back very upset because all the problems get jumbled up and many may not relate to them. I also don't believe patients should start to control the medical process."

On a personal level, Gnant has just cemented a very close relationship with industry by marrying his second wife, Claudia, who works for Merck, and he has two children from his first marriage. His greatest hobby at present looks to be clocking up air miles, which he would very much like to cut down on.

A key aim for the next few years is to push the clinical trial participation rate in Austria above 30%. "When we started it was just 5%, so I'm not going to believe in any ceiling," he says. His other desire is to see more taxpayer-funded research in Europe. There's no doubt he'd put the funds to good use.

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Breast Friend. This picture of Gnant, taken by the British portrait and fashion photographer Rankin, forms part of an exhibition of 'breast friends' organised by Europa Donna Austria (www.europadonna.at) to kick off breast cancer awareness month, October 2007

"We need more energy from more people and not organisations led for too long by the same people"